

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 10178.204WO	FOR FURTHER ACTION		See item 4 below
International application No. PCT/DK2004/000730	International filing date (<i>day/month/year</i>) 22 October 2004 (22.10.2004)	Priority date (<i>day/month/year</i>) 23 October 2003 (23.10.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant NOVOZYMES A/S			

<p>1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i>.1(a).</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																
<p>3. This report contains indications relating to the following items:</p> <table> <tr> <td><input checked="" type="checkbox"/> Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/> Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/> Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/> Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/> Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> <p>4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).</p>	<input checked="" type="checkbox"/> Box No. I	Basis of the report	<input checked="" type="checkbox"/> Box No. II	Priority	<input type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/> Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/> Box No. VI	Certain documents cited	<input type="checkbox"/> Box No. VII	Certain defects in the international application	<input type="checkbox"/> Box No. VIII	Certain observations on the international application
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<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 740 14 35</p>	<p>Date of issuance of this report 24 April 2006 (24.04.2006)</p>
	<p>Authorized officer</p> <p>Simin Baharlou</p> <p>Telephone No. +41 22 338 71 30</p>

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PATENT COOPERATION TREATY

REC'D 14 JAN 2005

WIPO

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/DK2004/000730

International filing date (day/month/year)
22.10.2004

Priority date (day/month/year)
23.10.2003

International Patent Classification (IPC) or both national classification and IPC
C12N9/58, C12N9/76, C11D3/386

Applicant
NOVOZYMES AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000730

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000730

Box No. II Priority

1. ☐ The following document has not been furnished:

- ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, Inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-4,7-9,12,13,16
	No: Claims	1,5,6,10,11,14,15,17-27
Inventive step (IS)	Yes: Claims	2-4,7-9,12,13,16
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-27
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/DK2004/000730

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: WO 95/30743 A (NOVONORDISK AS ; VON DER OSTEN CLAUS (DK);
FREDHOLM HENRIK (DK)) 16 November 1995 (1995-11-16)
D2: WO 88/07581 A (AMGEN INC) 6 October 1988 (1988-10-06)

1 Novelty (Art. 33(2) PCT)

Document D1 discloses a trypsin-like protease from *Fusarium oxysporum*, SEQ ID Nos: 1 and 2. Its protein sequence has 73.991% identity in a 223 amino acid overlap (26-248:1-221) with SEQ ID NO:2 of the present application which corresponds to a 73.009% identity calculated over the whole length of the protease (226 amino acids). Its DNA has 74.9% identity in a 744 nucleotide overlap with SEQ ID NO:1 (52-795:58-792). D1 further discloses variants with improved thermal, storage and/or protease stability (pp. 18ff), expression in *Aspergillus oryzae* and *Bacillus* (p.38) and the use of the protease in detergent (pp.41ff). The nucleic acid sequence from D1 will hybridize to the sequence of the present application. The protease from D1 is the same as used in the present application as a reference to show an improved stability in detergents (example V). As a result, D1 anticipates the subject matter of claims 1.a. and b., 5, 6, 10, 11, 14, 15.e. and 17 to 27 which is therefore not new under Art. 33(2) PCT.

2 Inventive Step (Art. 33(3) PCT)

2.1 D1 is the closest prior art and discloses a trypsin-like protease from *Fusarium oxysporum* from which the subject matter of the present application differs in that a different trypsin-like protease from *Fusarium solani* is provided.
The technical effect associated with said difference is the higher stability in detergents.

The problem to be solved is therefore the provision of a trypsin-like protease with an improved stability in detergents.

Although this problem was known in the art (see D2) the specific solution disclosed with the present application, namely the protease from *Fusarium solani*, has not been disclosed nor pointed to in the prior art. The skilled person was not directed by the prior art to this solution. Therefore, the protease of the present application is regarded to be inventive under Art. 33(3) PCT.

2.2 On the other, many claims are directed to variants of the protease defined by a percentage of identity, hybridizing nucleic acids or substituted/deleted/inserted amino acids. Many of these variants will not have the specific property of the protease, i.e. they will not show an improved stability in detergents compared to the reference proteases in the prior art (D1). This is apparent when considering that e.g. a 75% identical variant could be much closer to the protease from D1 (nearly identical) and will therefore show the lower activity. It is also a known fact that the exchange of only one amino acid (e.g. in the active site) can diminish the whole enzymatic activity. For any such variant that does not show the improved stability in detergents the problem to be solved would be the simple provision of a further protease variant which would not be inventive in view of D1 unless a surprising technical effect is associated with said variant.

No such variant has been disclosed in the present application. Therefore, only the specific protease defined by SEQ ID Nos: 1 and 2 is regarded to fulfill the inventive step criterion under Art. 33(3) PCT.

3 Industrial Application (Art. 33(4) PCT)

Apart from the above-mentioned novelty and inventive step objections the present claims fulfill the requirement of industrial applicability (Art. 33(4) PCT).

4 Clarity, Support, Disclosure (Art. 5, 6 PCT)

4.1 The subject matter of claims 6 and 7 refers to "mature part" of a protease without defining said term rendering said claims unclear under Art. 6 PCT.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/DK2004/000730

4.2 The subject matter of claims 12 and 13 use unusual parameters ("residual activity") and a reference to the description (only allowable if absolutely necessary, see Rule 6.2(a) PCT) rendering said claims unclear under Art. 6 PCT.

4.3 Claims 12 and 13 are not supported by the description as required by Art. 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following:

Said claims cover variants of the disclosed protease having an improved stability in detergents whereas no such variants have been disclosed and shown to work. The skilled person trying to perform the invention would be faced with undue burden generating all claimed variants and testing their stability in detergents. Therefore, only the specific protease defined by SEQ ID NOs: 1 and 2 is regarded to be technically supported under Art. 6 PCT.

4.4 The use of the term "hybridize under low/medium stringency conditions" used in claims 1.b., 10 and 15.e. renders the scope of said claim unclear under Art. 84 EPC as it is not clear how identical a sequence has to be in order to fall under the scope of said claim. The scope and meaning of a claim should be clear from the wording of the claim alone (Guidelines, 5.31), and an independent claim should specify clearly all of the essential features needed to define the invention (Guidelines, 3.3.3).

4.5 In claims 6 to 9 it is attempted to define the protease by reference to a clone present in a deposited E.coli strain. The sequence of the protease is not derivable from the application as filed using that definition. By contrast, the provided SEQ ID NOs. present in the application as filed clearly show the required sequences. Therefore, only a reference to said SEQ ID Nos is suitable to define the protease which renders the subject matter of claims 6 to 9 unclear under Art. 6 PCT.

4.6 In claim 15 subpoints a. to c. are missing rendering said claim unclear under Art. 6 PCT.